

Exhibit C 09/843,159



Protein

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1: P09874. Poly [ADP-ribose]...[gi:130781]

BLink, Domains, Links

LOCUS P09874 1014 aa linear PRI 15-SEP-2003

DEFINITION Poly [ADP-ribose] polymerase-1 (PARP-1) (ADPRT) (NAD+)
ADP-ribosyltransferase-1) (Poly[ADP-ribose] synthetase-1).

ACCESSION P09874

VERSION P09874 GI:130781

DBSOURCE swissprot: locus PPOL_HUMAN, accession P09874;

class: standard.

extra accessions:Q8IUZ9,created: Mar 1, 1989.

sequence updated: Dec 1, 1992.

annotation updated: Sep 15, 2003.

xrefs: gi: [510112](#), gi: [1017423](#), gi: [190166](#), gi: [190167](#), gi: [337423](#),
gi: [337424](#), gi: [178151](#), gi: [178152](#), gi: [190266](#), gi: [190267](#), gi:
[21693600](#), gi: [21693601](#), gi: [178188](#), gi: [178190](#), gi: [178167](#), gi:
[178168](#), gi: [178169](#), gi: [178170](#), gi: [178171](#), gi: [178172](#), gi: [178173](#),
gi: [178174](#), gi: [178175](#), gi: [178176](#), gi: [178177](#), gi: [178178](#), gi:
[178179](#), gi: [178180](#), gi: [178181](#), gi: [178182](#), gi: [178183](#), gi: [178185](#),
gi: [178186](#), gi: [178187](#), gi: [178166](#), gi: [178184](#), gi: [22902365](#), gi:
[22902366](#), gi: [35286](#), gi: [825702](#), gi: [35288](#), gi: [189535](#), gi: [189536](#),
gi: [627553](#)

xrefs (non-sequence databases): HSSPP26446, SWISS-2DPAGEP09874,
Aarhus/Ghent-2DPAGE1620, GenewHGNC:270, MIM [173870](#), GO0005634,
GO0003677, GO0003950, GO0008151, GO0006281, GO0006471, GO0006366,
InterProIPR001357, InterProIPR008288, InterProIPR001290,
InterProIPR004102, InterProIPR008893, InterProIPR001510,
PfamPF00533, PfamPF00644, PfamPF02877, PfamPF05406, PfamPF00645,
ProDomPD004675, SMARTSM00292, PROSITEPS50172, PROSITEPS00347,
PROSITEPS50064

KEYWORDS Transferase; Glycosyltransferase; NAD; DNA-binding; Nuclear
protein; ADP-ribosylation; Zinc-finger; Zinc; Polymorphism.

SOURCE Homo sapiens (human)

ORGANISM Homo sapiens

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE 1 (residues 1 to 1014)

AUTHORS Auer,B., Nagl,U., Herzog,H., Schneider,R. and Schweiger,M.

TITLE Human nuclear NAD+ ADP-ribosyltransferase(polymerizing):
organization of the gene

JOURNAL DNA 8 (8), 575-580 (1989)

MEDLINE [90091744](#)

PUBMED [2513174](#)

REMARK SEQUENCE FROM N.A.

REFERENCE 2 (residues 1 to 1014)

AUTHORS Uchida,K., Morita,T., Sato,T., Ogura,T., Yamashita,R., Noguchi,S.,
Suzuki,H., Nyunoya,H., Miwa,M. and Sugimura,T.

TITLE Nucleotide sequence of a full-length cDNA for human fibroblast
poly(ADP-ribose) polymerase

JOURNAL Biochem. Biophys. Res. Commun. 148 (2), 617-622 (1987)

MEDLINE [88076933](#)

PUBMED [3120710](#)

REMARK SEQUENCE FROM N.A.

TISSUE=Fibroblast

REFERENCE 3 (residues 1 to 1014)

AUTHORS Kurosaki,T., Ushiro,H., Mitsuuchi,Y., Suzuki,S., Matsuda,M.,
Matsuda,Y., Katunuma,N., Kangawa,K., Matsuo,H., Hirose,T.,
Inayama,S. and Shizuta,Y.

TITLE Primary structure of human poly(ADP-ribose) synthetase as deduced from cDNA sequence
JOURNAL J. Biol. Chem. 262 (33), 15990-15997 (1987)
MEDLINE 88058958
PUBMED 2824474
REMARK SEQUENCE FROM N.A.
TISSUE=Fibroblast

REFERENCE 4 (residues 1 to 1014)
AUTHORS Cherney,B.W., McBride,O.W., Chen,D.F., Alkhatib,H., Bhatia,K., Hensley,P. and Smulson,M.E.

TITLE cDNA sequence, protein structure, and chromosomal location of the human gene for poly(ADP-ribose) polymerase
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 84 (23), 8370-8374 (1987)
MEDLINE 88068596
PUBMED 2891139
REMARK SEQUENCE FROM N.A.

REFERENCE 5 (residues 1 to 1014)
AUTHORS Rieder,M.J., Livingston,R.J., Braun,A.C., Montoya,M.A., Chung,M.-W., Miyamoto,K.E., Nguyen,C.P., Nguyen,D.A., Poel,C.L., Robertson,P.D., Schackwitz,W.S., Sherwood,J.K., Witrak,L.A. and Nickerson,D.A.

TITLE Direct Submission
JOURNAL Submitted (~JUN-2002)
REMARK SEQUENCE FROM N.A.

REFERENCE 6 (residues 1 to 1014)
AUTHORS Strausberg,R.L., Feingold,E.A., Grouse,L.H., Derge,J.G., Klausner,R.D., Collins,F.S., Wagner,L., Shenmen,C.M., Schuler,G.D., Altschul,S.F., Zeeberg,B., Buetow,K.H., Schaefer,C.F., Bhat,N.K., Hopkins,R.F., Jordan,H., Moore,T., Max,S.I., Wang,J., Hsieh,F., Diatchenko,L., Marusina,K., Farmer,A.A., Rubin,G.M., Hong,L., Stapleton,M., Soares,M.B., Bonaldo,M.F., Casavant,T.L., Scheetz,T.E., Brownstein,M.J., Ustin,T.B., Toshiyuki,S., Carninci,P., Prange,C., Raha,S.S., Loquellano,N.A., Peters,G.J., Abramson,R.D., Mullahy,S.J., Bosak,S.A., McEwan,P.J., McKernan,K.J., Malek,J.A., Gunaratne,P.H., Richards,S., Worley,K.C., Hale,S., Garcia,A.M., Gay,L.J., Hulyk,S.W., Villalón,D.K., Muzny,D.M., Sodergren,E.J., Lu,X., Gibbs,R.A., Fahey,J., Helton,E., Kettelman,M., Madan,A., Rodrigues,S., Sanchez,A., Whiting,M., Madan,A., Young,A.C., Shevchenko,Y., Bouffard,G.G., Blakesley,R.W., Touchman,J.W., Green,E.D., Dickinson,M.C., Rodriguez,A.C., Grimwood,J., Schmutz,J., Myers,R.M., Butterfield,Y.S.N., Krzywinski,M.I., Skalska,U., Smailus,D.E., Schnerch,A., Schein,J.E., Jones,S.J.M. and Marra,M.A.

TITLE Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 99 (26), 16899-16903 (2002)
MEDLINE 22388257
PUBMED 12477932
REMARK SEQUENCE FROM N.A., AND VARIANT ALA-761.
TISSUE=Brain

REFERENCE 7 (residues 1 to 1014)
AUTHORS Suzuki,H., Uchida,K., Shima,H., Sato,T., Okamoto,T., Kimura,T. and Miwa,M.

TITLE Molecular cloning of cDNA for human poly(ADP-ribose) polymerase and expression of its gene during HL-60 cell differentiation
JOURNAL Biochem. Biophys. Res. Commun. 146 (2), 403-409 (1987)
MEDLINE 87298455
PUBMED 3113420
REMARK SEQUENCE OF 440-1013 FROM N.A.

REFERENCE 8 (residues 1 to 1014)
AUTHORS Suzuki,H., Uchida,K., Shima,H., Sato,T., Okamoto,T., Kimura,T. and Miwa,M.

JOURNAL Biochem. Biophys. Res. Commun. 148, 1549-1550 (1987)
REMARK ERRATUM.

REFERENCE 9 (residues 1 to 1014)
AUTHORS Yokoyama,Y., Kawamoto,T., Mitsuuchi,Y., Kurosaki,T., Toda,K., Ushiro,H., Terashima,M., Sumimoto,H., Kuribayashi,I., Yamamoto,Y.,

TITLE Maeda,T., Ikeda,H., Sagara,Y. and Shizuta,Y.
Human poly(ADP-ribose) polymerase gene. Cloning of the promoter region
JOURNAL Eur. J. Biochem. 194 (2), 521-526 (1990)
MEDLINE 91099327
PUBMED 2125269
REMARK SEQUENCE OF 1-94 FROM N.A.
REFERENCE 10 (residues 1 to 1014)
AUTHORS Ogura,T., Nyunoya,H., Takahashi-Masutani,M., Miwa,M., Sugimura,T. and Esumi,H.

TITLE Characterization of a putative promoter region of the human poly(ADP-ribose) polymerase gene: structural similarity to that of the DNA polymerase beta gene
JOURNAL Biochem. Biophys. Res. Commun. 167 (2), 701-710 (1990)
MEDLINE 90211250
PUBMED 2108670
REMARK SEQUENCE OF 1-39 FROM N.A.
REFERENCE 11 (residues 1 to 1014)
AUTHORS Herzog,H., Schneider,R., Hirsch-Kauffmann,M., Schnitzer,D. and Schweiger,M.

TITLE Direct Submission
JOURNAL Submitted (~JUL-1991)
REMARK SEQUENCE OF 1-39 FROM N.A.
REFERENCE 12 (residues 1 to 1014)
AUTHORS Gradwohl,G., Menissier de Murcia,J.M., Molinete,M., Simonin,F., Koken,M., Hoeijmakers,J.H. and de Murcia,G.

TITLE The second zinc-finger domain of poly(ADP-ribose) polymerase determines specificity for single-stranded breaks in DNA
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (8), 2990-2994 (1990)
MEDLINE 90222155
PUBMED 2109322
REMARK ANALYSIS OF ZINC FINGERS.
REFERENCE 13 (residues 1 to 1014)
AUTHORS Ikejima,M., Noguchi,S., Yamashita,R., Ogura,T., Sugimura,T., Gill,D.M. and Miwa,M.

TITLE The zinc fingers of human poly(ADP-ribose) polymerase are differentially required for the recognition of DNA breaks and nicks and the consequent enzyme activation. Other structures recognize intact DNA
JOURNAL J. Biol. Chem. 265 (35), 21907-21913 (1990)
MEDLINE 91072398
PUBMED 2123876
REMARK ANALYSIS OF ZINC FINGERS.
REFERENCE 14 (residues 1 to 1014)
AUTHORS Simonin,F., Menissier-de Murcia,J., Poch,O., Muller,S., Gradwohl,G., Molinete,M., Penning,C., Keith,G. and de Murcia,G.

TITLE Expression and site-directed mutagenesis of the catalytic domain of human poly(ADP-ribose)polymerase in Escherichia coli. Lysine 893 is critical for activity
JOURNAL J. Biol. Chem. 265 (31), 19249-19256 (1990)
MEDLINE 91035460
PUBMED 2121735
REMARK MUTAGENESIS OF CATALYTIC DOMAIN.
REFERENCE 15 (residues 1 to 1014)
AUTHORS Schreiber,V., Molinete,M., Boeuf,H., de Murcia,G. and Menissier-de Murcia,J.

TITLE The human poly(ADP-ribose) polymerase nuclear localization signal is a bipartite element functionally separate from DNA binding and catalytic activity
JOURNAL EMBO J. 11 (9), 3263-3269 (1992)
MEDLINE 92371433
PUBMED 1505517
REMARK NUCLEAR LOCALIZATION SIGNAL.
REFERENCE 16 (residues 1 to 1014)
AUTHORS Rolli,V., O'Farrell,M., Menissier-de Murcia,J. and de Murcia,G.

TITLE Random mutagenesis of the poly(ADP-ribose) polymerase catalytic domain reveals amino acids involved in polymer branching

JOURNAL Biochemistry 36 (40), 12147-12154 (1997)
 MEDLINE 97461532
 PUBMED 9315851
 REMARK MUTAGENESIS OF CATALYTIC DOMAIN.
 COMMENT

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[FUNCTION] Involved in the base excision repair (BER) pathway, by catalysing the poly(ADP-ribosyl)ation of a limited number of acceptor proteins involved in chromatin architecture and in DNA metabolism. This modification follows DNA damages and appears as an obligatory step in a detection/signaling pathway leading to the reparation of DNA strand breaks.
 [CATALYTIC ACTIVITY] NAD(+) + {ADP-D-ribosyl}(N)-acceptor = nicotinamide + {ADP-D-ribosyl}(N+1)-acceptor.
 [COFACTOR] Zinc, contains two moles of zinc per mole of protein.
 [SUBUNIT] Component of a base excision repair (BER) complex, containing at least XRCC1, PARP2, POLB and LIG3. Homo- and heterodimer with PARP2. Interacts with PARP3.
 [SUBCELLULAR LOCATION] Nuclear.
 [PTM] Poly-ADP-ribosylated by PARP2.
 [MISCELLANEOUS] The ADP-D-ribosyl group of NAD(+) is transferred to an acceptor carboxyl group on a histone or the enzyme itself, and further ADP-ribosyl groups are transferred to the 2'-position of the terminal adenosine moiety, building up a polymer with an average chain length of 20-30 units.
 [SIMILARITY] Belongs to the PARP family.
 [SIMILARITY] Contains 1 BRCT domain.

FEATURES	Location/Qualifiers
source	1..1014 /organism="Homo sapiens" /db_xref="taxon:9606"
gene	1..1014 /gene="ADPRT" /note="synonyms: PPOL, PARP1"
Protein	1..1014 /gene="ADPRT" /product="Poly [ADP-ribose] polymerase-1" /EC_number="2.4.2.30"
Site	2..372 /gene="ADPRT" /site_type="DNA binding"
Site	2 /gene="ADPRT" /site_type="blocked"
Region	17 /gene="ADPRT" /region_name="Conflict" /note="G -> E (IN REF. 3)."
Region	21..56 /gene="ADPRT" /region_name="Zinc finger region" /note="PARP-TYPE."
Region	70 /gene="ADPRT" /region_name="Conflict" /note="E -> Q (IN REF. 1 AND 2)."
Region	125..162 /gene="ADPRT" /region_name="Zinc finger region" /note="PARP-TYPE."
Region	188 /gene="ADPRT"

Region /region_name="Variant"
/note="A -> T (in dbSNP:1805409). /FTId=VAR_014714."
207..209
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/region_name="Domain"
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Region 212
/gene="ADPRT"
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/note="E -> K (IN REF. 3)."
Region 221..226
/gene="ADPRT"
/region_name="Domain"
/note="NUCLEAR LOCALIZATION SIGNAL 2ND PART."
Region 373..524
/gene="ADPRT"
/region_name="Domain"
/note="AUTOMODIFICATION DOMAIN."
Region 385..461
/gene="ADPRT"
/region_name="Domain"
/note="BRCT."
Site 407
/gene="ADPRT"
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/note="ADP-RIBOSYL[N] (POTENTIAL)."
Site 413
/gene="ADPRT"
/site_type="modified"
/note="ADP-RIBOSYL[N] (POTENTIAL)."
Site 435
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Site 437
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Site 444
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Site 456
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Site 471
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Site 484
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Site 488
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Site 491

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Site 513
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Site 514
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Site 520
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/ note="ADP-RIBOSYL[N] (POTENTIAL)."
Region 525..1014
/ gene="ADPRT"
/ region_name="Domain"
/ note="NAD-BINDING."
Region 613
/ gene="ADPRT"
/ region_name="Conflict"
/ note="H -> Q (IN REF. 4)."
Region 762
/ gene="ADPRT"
/ region_name="Variant"
/ note="V -> A (in dbSNP:1805412). /FTId=VAR_014715."
Site 797
/ gene="ADPRT"
/ site_type="mutagenized"
/ note="L->P: 1.5% OF WILD-TYPE ACTIVITY."
Region 827
/ gene="ADPRT"
/ region_name="Conflict"
/ note="N -> S (IN REF. 4)."
Site 868
/ gene="ADPRT"
/ site_type="mutagenized"
/ note="N->S: 4% OF WILD-TYPE ACTIVITY."
Site 890
/ gene="ADPRT"
/ site_type="mutagenized"
/ note="M->V: <0.5% OF WILD-TYPE ACTIVITY."
Site 893
/ gene="ADPRT"
/ site_type="mutagenized"
/ note="K->I: ABOLISHES ENZYMATIC ACTIVITY."
Site 897
/ gene="ADPRT"
/ site_type="mutagenized"
/ note="F->S: 10% OF WILD-TYPE ACTIVITY."
Site 899
/ gene="ADPRT"
/ site_type="mutagenized"
/ note="D->N: 0.6% OF WILD-TYPE ACTIVITY."
Region 908
/ gene="ADPRT"
/ region_name="Conflict"
/ note="C -> Y (IN REF. 4)."
Site 908
/ gene="ADPRT"
/ site_type="mutagenized"
/ note="C->R: <0.5% OF WILD-TYPE ACTIVITY."
Site 926
/ gene="ADPRT"
/ site_type="mutagenized"
/ note="L->F: 1.5% OF WILD-TYPE ACTIVITY."

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/note="K -> R (IN REF. 4)."
Region 980
/gene="ADPRT"
/region_name="Conflict"
/note="N -> I (IN REF. 4)."
Site 986
/gene="ADPRT"
/site_type="mutagenized"
/note="Y->H: 14% OF WILD-TYPE ACTIVITY AND INCREASED
BRANCHING 15-FOLD."
Site 988
/gene="ADPRT"
/site_type="mutagenized"
/note="E->K: 1.25% OF WILD-TYPE ACTIVITY; ONLY MONOMERS
ARE ADDED."
Site 1003
/gene="ADPRT"
/site_type="mutagenized"
/note="L->P: 1.5% OF WILD-TYPE ACTIVITY."

ORIGIN

```
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61 ghsirhpdve vdgfselrwd dqgkvkktae aggvtkgqgd gigskaekt1 gdfaaeyaks
121 nrstckgcm kiekgqvrls kkmvdpekpq lgmidrwyhp gcfvknreel gfrpeysasq
181 lkgsfllate dkealkkqlp gvksegkrkg devdgvdeva kkskkekdk dsklekalka
241 qndliwnikd elkkvcstnd lkellifnkq qvpsgesail drvadgmvmfg allpceecsg
301 qlvfksdayy ctgdvtawtk cmvktqtpnr kewvtpkefr eisylkklkv kkqdrifppe
361 tsasvaatpp pstasapaav nssasadkpl snmkiltlgk lsrnkdevka mieklggklt
421 gtankaslci stkkevekmn kkmeevkean irvvsedflq dvsastkslq elflahilsp
481 wgaevkaepv evvaprgksg aalskkskgq vkeeginkse krmkltlkgg aavdpdsgle
541 hsahvlekkg kvfsatlglv divkgtnsyy klqlleddke nrywifrswg rvgtvigsnk
601 leqmpskeda iehfmklyee ktgnawhskn ftkypkkfyp leidyggdee avkkltvnpq
661 tksklpkpvq dlikmifdve smkkamveye idlqkmpkgk lskrqiqaaay silsevqqav
721 sqgssdsqil dlsnrfytli phdfgmkkpp llnnadsvqa kvemldnlll ievaysllrg
781 gsddsskdpi dvnyeklktl ikvvdrdsee aeiirkyvkn thatthnayd levidifkie
841 regecqrykp fkqlhnrll whgsrttnfa gilsqglria ppeapvtgym fgkgyfadm
901 vsksanycht sqgdpigll lgevalgnmy elkhashisk lpkgkhsvkg lgkttpdpsa
961 nislsgvdpv lgtgissgvn dtsllyneyi vydiaqvnk yllklkfnfk tslw
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Jan 29 2004 15:38:25